Review Article

Endoscopic ultrasound for staging of colonic cancer proximal to the rectum: A systematic review and meta-analysis

Marie Louise Malmstrøm[1], Adrian Săftoiu[1,2], Peter Vilmann[1], Tobias Wirenfeldt Klausen[3], Ismail Gögenur[4]

[1]Department of Surgery, Endoscopy Unit, Herlev University Hospital, [3]Department of Haematology, Herlev University Hospital, Herlev, [4]Department of Surgery, Zealand University Hospital, University of Copenhagen, Køge, Denmark, [2]Research Center of Gastroenterology and Hepatology, University of Medicine and Pharmacy of Craiova, Craiova, Romania

ABSTRACT

Background and Objectives: Treatment of colonic cancer patients is highly dependent on the depth of tumor invasion (T-stage) as well as the extension of lymph node involvement (N-stage). We aimed to systematically review the accuracy of endoscopic ultrasound (EUS) for staging of colonic cancer proximal to the rectum. **Patients and Methods:** Men and women with colonic adenocarcinomas were included in the study. EUS staging was compared to histopathology as the gold standard. Outcome measures were T- and N-staging accuracies. Articles were searched in PubMed, Web of Science, The Cochrane Library, and EMBASE. **Results:** Six studies were identified comparing EUS staging of colonic cancer to histopathology. The pooled-staging sensitivity and specificity were 0.90 and 0.98 for T1 tumors, 0.67 and 0.96 for T2 tumors, and 0.97 and 0.83 for T3/T4 tumors, respectively. Sensitivity and specificity for N + disease were 0.59 and 0.78, respectively. **Conclusions:** EUS is a feasible method for T-staging of cancers of the colon proximal to the rectum. The accuracy of lymph node staging needs to be verified by prospective multicenter studies including larger patient populations.

Key words: Colonic cancer, endoscopic ultrasound, staging, systematic review

INTRODUCTION

Colorectal carcinoma represents a global health burden as the most common cancer of the digestive tract. It is the third most frequent cancer diagnosed in males and the second in females.[1] Preoperative status of tumor invasion depth is important for the selection of endoscopic treatment or surgical resection. In addition, stratification based on stage is also important for selecting patients to the established neoadjuvant radiochemotherapy for rectal cancer and promising neoadjuvant chemotherapy for patients with colon cancer.[2] In rectal cancer, transluminal endoscopic microsurgery has shown to be an effective and

Access this article online

Quick Response Code:

Website: www.eusjournal.com

DOI: 10.4103/2303-9027.191610

How to cite this article: WMalmstrom ML, Saftoiu A, Vilmann P, Klausen TW, Gogenur I. Endoscopic ultrasound for staging of colonic cancer proximal to the rectum: A systematic review and meta-analysis. Endosc Ultrasound 2016;5:307-14.

Address for correspondence

Dr. Marie Louise Malmstrøm, Department of Surgery, Endoscopy Unit, Herlev University Hospital, Herlev, Denmark.

E-mail: malmstroem@gmail.com

Received: 2015-08-23; **Accepted:** 2016-04-22

safe procedure for selected patients.[3] The value of transrectal ultrasound (TRUS) for the staging of rectal cancer has been investigated in numerous studies. Thus, TRUS has become the method of choice for locoregional T-staging of rectal cancer while N-staging needs further refinement in diagnostic criteria and endoscopic ultrasound (EUS) technology to improve diagnostic accuracy.[4-6] Only limited literature exists concerning colonic neoplasms.

In this systematic review, we aimed to systematically review the literature assessing the value of EUS-based staging of malignant colonic neoplasms compared to histological stage.

PATIENTS AND METHODS

The review was conducted according to the PRISMA guidelines[7] (PROSPERO registration number: CRD42015016013). Literature search was performed in June 2015 in PubMed (1946–2015), EMBASE (1980–2015), Web of Science (1900–2015), and The Cochrane Library (1972–2015) [Figure 1]. A search was performed using the following MeSH terms: [colon cancer], [colonic neoplasms], [colon neoplasms], [colonic cancer] and [endoscopic ultrasound], [ultrasonography] using the Boolean operators OR/AND. Two authors individually assessed all abstracts found in the primary search (MLM, IG). English, German, and French studies were evaluated. A "snowball" search was manually performed from the reference lists of included studies. Finally, all included studies were crosschecked in Web of Science under "citations."

Data regarding study characteristics, diagnostic methods, and accuracies of T- and N-stages with histology as controls were extracted. Studies with combined accuracies for rectum and colon were only included if the colonic data could be separated from the rectum data. Authors of studies with mixed data where separation was not obvious were contacted. For each separate study, characteristics such as demography, study design, inclusion and exclusion criteria, patient numbers, sample size calculations, and endpoints were evaluated and are presented in Table 1. Data on endoscopic equipment, operator experience, blinding, measure categorization, adverse events, missing data, and treatment and comparisons to other diagnostic modalities are presented in Table 2. Studied data are referred to without interpretation.

There is no consensus on the assessment of the quality of clinical studies lacking a control arm;[8] however, we chose to include studies based on inclusion criteria and completeness of data as well as to assess the risk of bias in each individual study. The guidelines from the (STARD) The Standards for Reporting of Diagnostic Accuracy

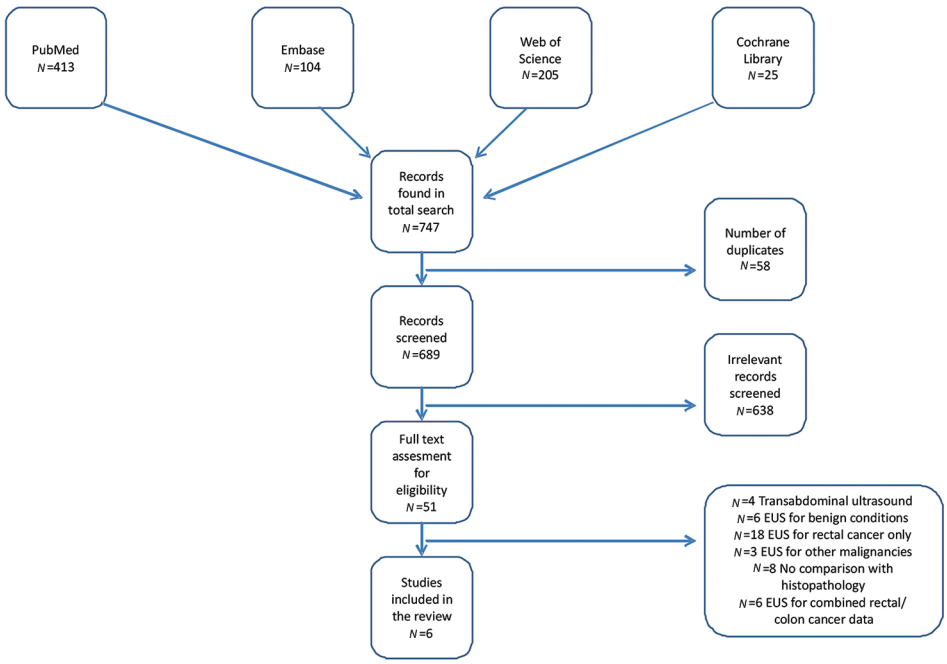

Figure 1. Flowchart on the search strategy

Table 1. Schematic setup summarizing the study characteristics and design including inclusion and exclusion criteria, demography, number of patients, sample size, and endpoints for the different studies

Study	Study characteristics						
	Demography	Design	Inclusion criteria	Exclusion criteria	Patients, *n*	Sample size	Endpoints
Stergiou	Men and women	Prospective trial	Patients awaiting laparoscopic or endoscopic resection of colonic cancer	Locally advanced tumors or systemic spread of tumor	33	Not described	Diagnostic accuracy, T-and N-stage
Kuntz	Men and women, ulcerative colitis + familiar polyposis overrepresented	Prospective trial	EUS performed in patients where it was expected that there would be therapeutic implications. Inclusion from February 1995 to December 1996	Not fulfilling the inclusion criteria	23	Not described	Diagnostic accuracy, T- and N-stage
Kongkam	Men (11), women (10)	A retrospective study with prospectively entered database	Patients aged 18-80, with colonic cancer and endoscopic or surgical resection scheduled within 4 weeks. Inclusion from March 2012 to February 2013	Contraindications for surgery or EUS examination	21	Not described	Diagnostic accuracy, T- and N-stage
Lok Tio	Men (17), women (13)	Prospective trial	EUS performed 1-4 weeks prior to colonic cancer surgery. Inclusion from March 1984 to October 1989	Not fulfilling inclusion criteria	30	Not described	Diagnostic accuracy, T- and N-stage
Tseng	Men and women	Prospective trial	Patients with biopsy-proven colorectal carcinoma	Not fulfilling inclusion criteria	29	Not described	Diagnostic accuracy, T- and N-stage
Haji	Men and women	Prospective trial	Patients listed for surgical resection of a colon cancer. Inclusion from March 2008 to April 2009	Not fulfilling the inclusion criteria	38	Not described	Diagnostic accuracy, T- and N-stage with EUS and CT
Haji	As above	As above	As above	As above	34	As above	As above

EUS: Endoscopic ultrasound, CT: Computed tomography

initiative have been used to evaluate the completeness of reporting in studies on diagnostic accuracy [Tables 1 and 2], as well as to assess bias.[9]

Statistical analysis

Pooled estimates of sensitivity and specificity were calculated using the Rutter and Gatsonis Hierarchical Summary Receiver Operating Characteristic (HSROC) model.[10,11] Possibly due to the limited number of studies and high proportions of studies having a specificity at 1 for the T2 tumors, the random effect model failed to fit. Assumptions for using the Rutter and Gatsonis HSROC model might be violated as the T2s have two thresholds, both toward T3 and T1. In this case, a fixed effect model was used for estimating sensitivity and specificity. Sensitivity and specificity were given with a 95% confidence interval (CI). Data were entered in RevMan 5.3 (Review Manager Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and used for drawing the figures. Calculations of pooled sensitivity and specificity were performed using the SAS macro MetaDas 1.3 (User Guide Version 1.3. 2010 July; available from: http://srdta.cochrane.org/ref) on SAS version 9.4 (SAS Institute Inc., 2012, Cary, NC, USA).

RESULTS

The initial search proposed 747 articles, with 58 excluded as duplicates, 638 irrelevant records, and 51 assessed for full-text eligibility. Of these, only six were relevant.[12-17] A flow chart of the search strategy is presented in Figure 1. Six potential studies were excluded from the study due to data on colonic cancers alone could not be provided. One author provided separate tumor node metastasis classified data for colonic tumors but only included adenomas and very early cancers and was excluded from this review.[18] Other authors of mixed data studies were unable to provide information on colon cancer patients alone or did not reply. The latter studies were excluded from the review.

The total number of patients with colonic cancers evaluated for T-stage with EUS and with surgical pathology at the gold standard was 208. The study by Haji *et al.* counted as two studies due to the same patient population was evaluated with two ultrasound frequencies with each set of data calculated separately.[17] None of the studies reported any complication due to the diagnostic procedures either with miniprobes[12,16,17]

Table 2. Summary of the diagnostic methods for the different studies with emphasis on endoscopes and operators, blinding, classification systems, adverse events, missing data, treatment of the patients, and comparison of endoscopic ultrasound to different diagnostic modalities

Study	Diagnostic methods						
	Endoscopes	Blinding	Categorization of measures	Adverse events	Missing data	Treatment	Other diagnostic modalities
Stergiou	UM2-R, Olympus optical miniprobe, 12 mHz	Not described	TNM classification	Not described	Insufficient water filling in 3 patients + 1 patient excluded for technical reasons	T1, N0 tumors: endoscopic resection. T2-T3, N0 tumors, laparoscopic resection (if 10 cm margin to the flexuras), all other tumors got resected by open surgery	None
Kuntz	CF-UM20 Olympus optical radial 320°, 12 mHz	Not described	TNM classification	Not described	Not described	Not described	None
Kongkam	EG-530 UR2 forward viewing radial 5, 7.5, 10, 12 mHz	Endoscopist blinded to CT findings	TNM classification. Location, tumor invasion circumferential involvement, ability to pass the lesion and duration of the procedure	No adverse events	None	All patients were operated and full histological specimens obtained	EUS staging compared to the CT scan
Lok Tio	EU-M2/M3 Olympus, side viewing radial array/XCF-UM2 Olympus, forward viewing radial array both 180°/360°, 7.5 mHz	Not described	TNM classification. Lymph node definitions: N0 hyperechoic with indistinct boundaries, N1+N2 hypoechoic with defined boundaries	None	Not described	All patients were operated and full histological specimens obtained	None
Tseng	UM2-R Olympus, optical miniprobe and inflated balloon sheath 12 mHz	Not described	TNM classification	Not described	Three cases were excluded due to stenosis and bends	Six T1 patients received EMR, 80 patients had exploratory laparotomy+tumor resection	None
Haji	Keymed Olympus, high-frequency miniprobe 12 mHz	Endoscopists (2) present at EUS, for stage consensus. They were blinded to CT	TNM classification. Positive nodal metastases on CT scan defined as a single node >1 cm or a cluster of three nodes each >3 mm. Defined hypoechoic nodes on EUS were considered positive	Not described	38 patients (12 mHz) and 34 patients (20 mHz), no description why	All patients underwent surgical resection with full histology	EUS staging compared to the CT scan
Haji	As above, but 20 mHz	As above	As above	As above	As above	As above	As above

CT: Computed tomography, EUS: Endoscopic ultrasound, TNM: Tumor node metastasis, EMR: Endoscopic mucosal resection

or with radial transducers.[13-15] Some, however, had to give up tumor staging due to technical difficulties; these were not included in our analysis.[12,16]

In terms of N-stage, most studies evaluated this parameter based on histology of the surgical resection specimen after laparoscopy or open surgery. Two studies adjusted for local resections.

The T- and N-stages from the six analyzed studies were as follows:

- T1: A summary of the studies for patients with T1 disease is shown in Figure 2a. The pooled sensitivity was 0.90 (95% CI: 0.66–0.98) and the specificity was 0.98 (95% CI: 0.94–0.996)
- T2: A summary of the studies for patients with T2 disease is shown in Figure 2b. The pooled sensitivity and specificity were calculated using a simple fixed effect model. The pooled sensitivity was 0.67 (95% CI: 0.50–0.80) and the specificity was 0.96 (95% CI: 0.92–0.98)
- T3/T4: A summary of the studies for patients with T3/T4 disease is shown in Figure 2c. The pooled sensitivity was 0.97 (95% CI: 0.88–0.99) and the specificity was 0.83 (95% CI: 0.73–0.90)
- N: A summary of the studies for patients with

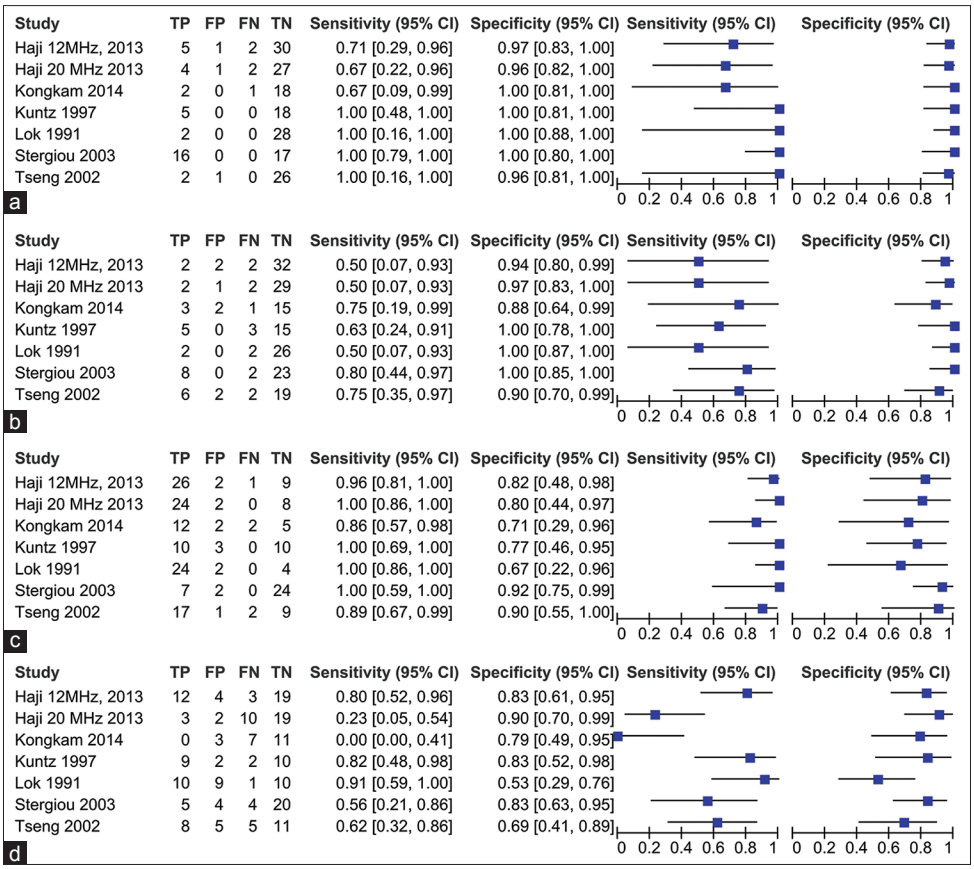

Figure 2. Forest plot with a cross table on included patients for diagnostic accuracy measurements for endoscopic ultrasound in comparison to histology for (a) T1, (b) T2, (c) T3/4, and (d) lymph node positive patients. Sensitivity and specificity with 95% confidence intervals have been given in numbers as well as illustrated graphically

N-positive disease is shown in Figure 2d. The pooled sensitivity was 0.59 (95% CI: 0.31–0.82) and the specificity was 0.78 (95% CI: 0.68–0.86).

DISCUSSION

The aim of this systematic review was to assess the diagnostic accuracy of EUS for staging of malignant colonic tumors proximal to the rectum. Six studies, evaluating 208 patients with colonic cancer, in terms of tumor stage compared to pathological stage, were identified and sensitivity and specificity on T- and N-stages were calculated. T-staging with EUS of colonic and rectal tumors can be compared in terms of accuracies.[19,20] For rectal tumors, EUS in early tumors (T1/2) has been considered the staging modality of choice.[21]

At present, the image modality of choice for staging of colonic cancer is a CT-scan. The study by Haji *et al.* is a comparative study between the image modalities of CT and miniprobe EUS. The EUS was found to be significantly more accurate in the local staging of both early and advanced tumors.[17] There is an ongoing prospective, randomized trial,[2] evaluating neoadjuvant chemotherapy in locally advanced operable T3/T4 colonic tumors. Neoadjuvant therapy may target micrometastatic disease earlier, downstage tumor, as well as reduce surgical tumor cell shedding.[22] If operable, T3/T4 cancers will benefit from neoadjuvant therapy. The accuracy of staging will become even more important, allowing quicker assignment to correct multimodal treatment.

The results of this review have to be interpreted in the context of limitations of the calculations and the risk of bias in the systematic review and its sources. Tables 1 and 2 illustrate some heterogeneity in study designs: The resection methods as well as the operator dependency using the EUS technique. Only a few of the studies mention blinding concerning pathologists and endoscopists,[14,17] which may potentially lead to differentiated and nondifferentiated informational bias. Selection bias undoubtedly occurs since some studies include highly selected patients.[12,13] None of the studies described power calculations made prior

to the inclusion. This may increase the risk of type II errors due to the lack of statistical power, especially considering the small numbers of patients in most studies.[23]

Comparing different types of endoscopes and frequencies could also affect the results. It is argued that staging by miniprobe is advantageous in staging of stenotic tumors because the miniprobe, which is passed through the biopsy channel of an ordinary colonoscope, is highly successful in passing stenotic lesions in contrast to conventional EUS endoscopes.[24] Some studies emphasize that miniprobes are also useful for staging of small and flat lesions.[16] Miniprobes however using high ultrasonic frequency with low penetration depth will not be able to examine all layers of the colonic wall or lymph nodes. This is especially true for advanced cancers that infiltrate deeper layers.[25] Conventional EUS may pose difficulties in obtaining cross-sectional images over lesions located over a colonic bend or in strictures.[16] Others argue that a radial echoendoscope can be considered a feasible staging instrument for colonic cancers in all sections of the colon.[14] Authors state following reasons for staging inaccuracy: (1) presence of inflammation in the subserosal layer as a reason for overstaging T1 to T2[15] and (2) understaging of T2 and T3 tumors primarily due to difficulties in distinguishing carcinomatous microinfiltration from inflammatory changes.[13,16] Overall, only very few T4 tumors were evaluated. This may be due to the fact that T4 tumors have a high risk of stenosis and are therefore difficult to evaluate by EUS.

EUS in general is a standard procedure for staging of many gastrointestinal lesions,[26-28] and an EUS examination of the entire colon has been shown to be technically feasible and safe.[29,30] Due to the colorectal screening programs, an increasing number of tumors of the colon is found at earlier stages.[31] This fact, combined with a population of increasing age with higher risks of comorbidity, puts clinicians in therapeutic dilemmas. For elderly comorbid patients who are questionable candidates for major surgery, EUS could possibly open a new avenue for treatment decisions such as small local tumor resections, or in the near future, full-thickness endoscopic resection as a routine procedure,[32] based on T-staging evaluation with exclusion of local lymph node metastases. The latter evaluation is a challenge at present as N-staging significantly impacts colonic cancer management and imaging methods used today are inaccurate.[33,34] Further studies should be undertaken in the future with larger numbers of patients to clarify whether EUS will prove useful for staging of cancer of the colon.

Apart from therapeutic stratification to neoadjuvant chemoradiation, preoperative TN-staging of colorectal cancers is also of importance for prognostication.[14,18,35] Consequently, there is also at present interest in other imaging methods to additionally subclassify these cancers. Evaluation of tumor vascularity by EUS is such a method that may be useful both for prognostication and for assessment of the efficacy of antiangiogenic agents early in the course of therapy.[36,37] Imaging and evaluation of the blood flow velocity and direction can be carried out using Doppler sonography.[38] The feasibility of contrast-enhanced EUS (CE-EUS) examinations with second-generation microbubble contrast agents used as Doppler signal enhancers was proven by several groups.[39,40] Evaluation of tumor perfusion can also be performed by low mechanical CE-EUS.[41] According to the European Federation Societies in Ultrasound in Medicine and Biology guidelines, CE-EUS can be utilized to assess early response to biologic therapy in tumors, such as metastatic gastrointestinal stromal tumor, renal cell carcinoma, and hepatocellular carcinoma.[42,43] A similar approach has recently been described for quantitative assessment of tumor perfusion in colorectal cancer.[36]

Very few studies have evaluated the use of EUS for staging of malignant colonic neoplasms. Accurate staging of colonic cancer proximal to the rectum is becoming increasingly important for treatment decisions in the setting of modern oncology and technical advancements in surgery and endoscopy. EUS may become an important imaging modality in the determination of the therapeutic approach to patients with colon cancer; however, further large multicenter trials are necessary before firm conclusions can be drawn, especially regarding evaluation of the N-stage.

CONCLUSION

Very few studies have evaluated the use of EUS for staging of malignant colonic neoplasms. Accurate staging of colonic cancer proximal to the rectum is becoming increasingly important for treatment decisions

in the setting of modern oncology and technical advancements in surgery and endoscopy. In this study we found the pooled-staging sensitivity and specificity to be 0.90 and 0.98 for T1 tumors, 0.67 and 0.96 for T2 tumors, and 0.97 and 0.83 for T3/T4 tumors, respectively. Concerning N+ disease, the sensitivity and specificity was 0.59 and 0.78, respectively. EUS may become an important imaging modality in the determination of the therapeutic approach to patients with colon cancer; however, further large multicenter trials are necessary before firm conclusions can be drawn, especially regarding evaluation of the N-stage.

Acknowledgments

We thank Janne Wendt Librarian at Herlev Hospital for her help in relation to literature search.

Financial support and sponsorship

The study was partially funded by Agnes and Poul Friis Fund, Astrid Thaysens Legat, Axel Muusfeldts Fund, Dansk Medicinsk Selskab, Krista and Viggo Petersens Fund, Arvid Nilssons Fund, Director Jacob Madsens and wife Olga Madsens Fund, Director Svend Espersens Fund, Lykfeldts Fund, and the Research Councils of Herlev and Køge Hospitals.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Jemal A, Bray F, Center MM, *et al.* Global cancer statistics. *CA Cancer J Clin* 2011;61:69-90.
2. Foxtrot Collaborative Group. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: The pilot phase of a randomised controlled trial. *Lancet Oncol* 2012;13:1152-60.
3. Guerrieri M, Gesuita R, Ghiselli R, *et al*. Treatment of rectal cancer by transanal endoscopic microsurgery: Experience with 425 patients. *World J Gastroenterol* 2014;20:9556-63.
4. Puli SR, Bechtold ML, Reddy JB, *et al*. How good is endoscopic ultrasound in differentiating various T stages of rectal cancer? Meta-analysis and systematic review. *Ann Surg Oncol* 2009;16:254-65.
5. Puli SR, Reddy JB, Bechtold ML, *et al.* Accuracy of endoscopic ultrasound to diagnose nodal invasion by rectal cancers: A meta-analysis and systematic review. *Ann Surg Oncol* 2009;16:1255-65.
6. Kav T, Bayraktar Y. How useful is rectal endosonography in the staging of rectal cancer? *World J Gastroenterol* 2010;16:691-7.
7. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *J Clin Epidemiol* 2009;62:1006-12.
8. Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group. *JAMA* 2000;283:2008-12.
9. Smidt N, Rutjes AW, van der Windt DA, *et al.* Reproducibility of the STARD checklist: An instrument to assess the quality of reporting of diagnostic accuracy studies. *BMC Med Res Methodol* 2006;6:12.
10. Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10: Analysing and Presenting Results. In: Deeks JJ, Bossuyt PM, Gatsonis C (editors), Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0. The Cochrane Collaboration, 2010. Available from: http://methods.cochrane.org/sdt/sites/methods.cochrane.org.sdt/files/uploads/Chapter%2010%20-%20Version%201.0.pdf. [Last accessed on 2016 Aug 22].
11. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med* 2001;20:2865-84.
12. Stergiou N, Haji-Kermani N, Schneider C, *et al*. Staging of colonic neoplasms by colonoscopic miniprobe ultrasonography. *Int J Colorectal Dis* 2003;18:445-9.
13. Kuntz C, Kienle P, Buhl K, *et al*. Flexible endoscopic ultrasonography of colonic tumors: Indications and results. *Endoscopy* 1997;29:865-70.
14. Kongkam P, Linlawan S, Aniwan S, *et al*. Forward-viewing radial-array echoendoscope for staging of colon cancer beyond the rectum. *World J Gastroenterol* 2014;20:2681-7.
15. Tio TL, Coene PP, van Delden OM, *et al*. Colorectal carcinoma: Preoperative TNM classification with endosonography. *Radiology* 1991;179:165-70.
16. Tseng LJ, Jao YT, Mo LR. Preoperative staging of colorectal cancer with a balloon-sheathed miniprobe. *Endoscopy* 2002;34:564-8.
17. Haji A, Ryan S, Bjarnason I, *et al*. Colonoscopic high frequency mini-probe ultrasound is more accurate than conventional computed tomography in the local staging of colonic cancer. *Colorectal Dis* 2012;14:953-9.
18. Shimura T, Ebi M, Yamada T, *et al.* Magnifying chromoendoscopy and endoscopic ultrasonography measure invasion depth of early stage colorectal cancer with equal accuracy on the basis of a prospective trial. *Clin Gastroenterol Hepatol* 2014;12:662-8.e1-2.
19. Gall TM, Markar SR, Jackson D, *et al*. Mini-probe ultrasonography for the staging of colon cancer: A systematic review and meta-analysis. *Colorectal Dis* 2014;16:O1-8.
20. Frascio F, Giacosa A. Role of endoscopy in staging colorectal cancer. *Semin Surg Oncol* 2001;20:82-5.
21. Wald C, Scheirey CD, Tran TM, *et al.* An update on imaging of colorectal cancer. *Surg Clin North Am* 2006;86:819-47.
22. Nelson H, Petrelli N, Carlin A, *et al.* Guidelines 2000 for colon and rectal cancer surgery. *J Natl Cancer Inst* 2001;93:583-96.
23. Mittendorf R, Arun V, Sapugay AM. The problem of the type II statistical error. *Obstet Gynecol* 1995;86:857-9.
24. Hünerbein M, Totkas S, Ghadimi BM, *et al*. Preoperative evaluation of colorectal neoplasms by colonoscopic miniprobe ultrasonography. *Ann Surg* 2000;232:46-50.
25. Rafaelsen SR, Vagn-Hansen C, Sørensen T, *et al*. Transrectal ultrasound and magnetic resonance imaging measurement of extramural tumor spread in rectal cancer. *World J Gastroenterol* 2012;18:5021-6.
26. Gonzalo-Marin J, Vila JJ, Perez-Miranda M. Role of endoscopic ultrasound in the diagnosis of pancreatic cancer. *World J Gastrointest Oncol* 2014;6:360-8.
27. Ahuja NK, Sauer BG, Wang AY, *et al*. Performance of endoscopic ultrasound in staging rectal adenocarcinoma appropriate for primary surgical resection. *Clin Gastroenterol Hepatol* 2015;13:339-44.
28. Giganti F, Orsenigo E, Arcidiacono PG, *et al.* Preoperative locoregional staging of gastric cancer: Is there a place for magnetic resonance imaging? Prospective comparison with EUS and multidetector computed tomography. *Gastric Cancer* 2016;19:216-25.
29. Bhutani MS, Nadella P. Utility of an upper echoendoscope for endoscopic ultrasonography of malignant and benign conditions of the sigmoid/left colon and the rectum. *Am J Gastroenterol* 2001;96:3318-22.
30. Nguyen-Tang T, Shah JN, Sanchez-Yague A, *et al*. Use of the front-view forward-array echoendoscope to evaluate right colonic subepithelial lesions. *Gastrointest Endosc* 2010;72:606-10.
31. Toh EW, Brown P, Morris E, *et al.* Area of submucosal invasion and width of invasion predicts lymph node metastasis in pT1 colorectal cancers. *Dis Colon Rectum* 2015;58:393-400.
32. Schmidt A, Bauerfeind P, Gubler C, *et al*. Endoscopic full-thickness resection in the colorectum with a novel over-the-scope device: First experience. *Endoscopy* 2015;47:719-25.

33. Nørgaard A, Dam C, Jakobsen A, *et al*. Selection of colon cancer patients for neoadjuvant chemotherapy by preoperative CT scan. *Scand J Gastroenterol* 2014;49:202-8.
34. Lim M, Hussain Z, Howe A, *et al.* The oncological outcome after right hemicolectomy and accuracy of CT scan as a preoperative tool for staging in right sided colonic cancers. *Colorectal Dis* 2013;15:536-43.
35. Mukae M, Kobayashi K, Sada M, *et al*. Diagnostic performance of EUS for evaluating the invasion depth of early colorectal cancers. *Gastrointest Endosc* 2015;81:682-90.
36. Cartana ET, Streata I, Nicoli ER, *et al.* Evaluation of tumour angiogenesis in colorectal cancer based on quantitative contrast – Enhanced endoscopic ultrasonography and molecular analysis. *Gastrointest Endosc* 2015;81: AB175. Available from: http://www.giejournal.org/article/S0016-5107(15) 02176-8/fulltext. [Last accessed on 2015 Jul 15].
37. Cartana T, Brink L, Streba CT, *et al*. Low mechanical index contrast – Enhanced endoscopic ultrasound for quantitative assessment of tumour perfusion in colorectal cancer patients: Preliminary study. *Gastrointest Endosc* 2014;79:AB405. Available from: http://www.giejournal. org/article/S0016-5107(14) 00701-9/fulltext. [Last accessed on 2015 Jul 15].
38. Sanchez MV, Varadarajulu S, Napoleon B. EUS contrast agents: What is available, how do they work, and are they effective? *Gastrointest Endosc* 2009;69 2 Suppl: S71-7.
39. Dietrich CF, Ignee A, Braden B, *et al*. Improved differentiation of pancreatic tumors using contrast-enhanced endoscopic ultrasound. *Clin Gastroenterol Hepatol* 2008;6:590-7.e1.
40. Saftoiu A, Iordache SA, Gheonea DI, *et al.* Combined contrast-enhanced power Doppler and real-time sonoelastography performed during EUS, used in the differential diagnosis of focal pancreatic masses (with videos). *Gastrointest Endosc* 2010;72:739-47.
41. Saftoiu A, Vilmann P, Dietrich CF, *et al.* Quantitative contrast-enhanced harmonic EUS in differential diagnosis of focal pancreatic masses (with videos). *Gastrointest Endosc* 2015;82:59-69.
42. Piscaglia F, Nolsøe C, Dietrich CF, *et al*. The EFSUMB guidelines and recommendations on the clinical practice of contrast enhanced ultrasound (CEUS): Update 2011 on non-hepatic applications. *Ultraschall Med* 2012;33:33-59.
43. Lassau N, Koscielny S, Chami L, *et al.* Advanced hepatocellular carcinoma: Early evaluation of response to bevacizumab therapy at dynamic contrast-enhanced US with quantification – Preliminary results. *Radiology* 2011;258:291-300.